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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,847	08/13/2001	Steen Troels Jorgensen	10022,204-US	9117

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EXAMINER

LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	1Q

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/928,847	JORGENSEN ET AL.
	Examiner David A. Lambertson	Art Unit 1636

-- The MAILING DATE of this communication appears in the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 16 May 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 67-87 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 67-87 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Receipt is acknowledged of a reply, filed May 16, 2003 as Paper No. 14, to the previous Office Action. Amendments were made to the claims. Specifically, claims 1-5, 30-44, 63 and 66 were cancelled and claims 67-87 were added.

Claims 67-87 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, Paper No. 13, mailed December 17, 2003, that is not addressed in this action has been withdrawn.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed on June 12, 2003 as Paper No. 15.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 recites the limitation "wherein the bacterial host cell had a copy of the gene in the chromosome prior to integration" in lines 14-15 of the claim. There is insufficient antecedent basis for this limitation in the claim. It is unclear if the claim is referring to the "gene of interest" or if it is referring to the non-functional gene.

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Claim 77 recites a method for producing a bacterial host cell comprising at least two copies of a gene of interest stably integrated into the chromosome at different positions, but lacks a positive process step in the method whereby a bacterial host cell is produced. In the absence of a step recapitulating the preamble of the claim, the method has no final step, therefore the metes and bounds of the claim are indefinite. It would be remedial to include a step such as, "whereby a bacterial host cell comprising at least two copies of a gene of interest stably integrated into the chromosome at different positions is produced."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67-69, 71-79 and 81-87 are rejected under 35 U.S.C. 102(e) as being anticipated by Rasmussen (US 2003/044940; see entire document).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Rasmussen discloses a method of increasing the number of copies of a gene of interest, wherein the gene of interest is contained within an “amplification unit” (see for example paragraph [0082], page 6). This is done by integrating the amplification unit into the chromosome of a host cell (see for example paragraph [0098], page 8), and since the method of Rasmussen is drawn to a method of increasing the number of copies of the amplification unit in the chromosome of a host cell, the host cell must necessarily have a copy already present in the chromosome. The integration into the chromosome is achieved by first rendering a conditionally essential host gene non-functional to make the host cell selectable, and then targeting the amplification unit to the non-functional host gene by including a likewise non-functional copy of the same conditionally essential host gene (which is non-functional for a different biochemical reason) on the amplification unit (see for example paragraph [0115], page 9). This then allows homologous recombination to occur between the amplification unit and the two different non-functional conditionally essential genes, thereby restoring the functionality of the conditionally essential gene, and allowing for a selection of the integrated host cell that now also includes a copy of the amplification unit (see for example paragraphs [0115-0117]). This amplification unit can also contain a nucleotide sequence with homology to a separate chromosomal nucleotide sequence so as to improve the frequency of homologous recombination between the amplification unit and the host chromosome (see for example paragraphs [0080] and [0114]). Rasmussen also anticipates performing multiple cycles of the integration process in order to increase the copy number of the amplification unit/gene of interest (see for example paragraph [0031], page 2). In some embodiments, the amplification unit also contains an antibiotic resistance gene, including ampicillin or kanamycin (see for example paragraph [0077], page 5),

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flanked by resolvase sites to excise the resistance gene from the chromosome following integration (see for example paragraph [0118]). Additionally, the conditionally essential gene can be rendered non-functional by partial deletion (see for example paragraph [0116], page 9). Furthermore, Rasmussen contemplates the use of Bacillus host cells for this purpose, including *Bacillus licheniformis* (see for example paragraph [0100], page 8). Thus, Rasmussen contemplates the method of making host cells in the same manner as claimed in the instant application, and therefore anticipates the invention as it regards making the cells and the cells themselves. Finally, Rasmussen teaches using these cells in a process for producing the protein of interest, encoded by the gene of interest as contained in the amplification unit (see for example paragraph [0039], page 2).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 67, 68 and 71-76 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 59 in view of claims 1, 4, 16, 17 and 19 of copending Application No. 09/869,855 (US 2003/0044940; Rasmussen, as

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above; henceforth the ‘855 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 67, 68 and 71-76 of the instant application describe a method of using a particular host cell to make a protein, while the combination of claim 59 in view of claims 1, 4, 16, 17 and 19 of the ‘855 application describes a similar invention.

The rejection is based on the fact that claim 67 is a process (method of making a protein) that uses a “product-by-process” (the host cell). In essence, the method is drawn to producing a protein using a host cell which comprises at least two copies of a gene of interest, wherein the gene of interest is stably integrated into the chromosome. The process by which the host cell is generated has very little patentable weight because the method is directed to using the cell, not making the cell, and the cell can be made by different methods. The same rationale is true of claim 59 in the ‘855 patent.

Claim 59 of the ‘855 application recites a method of making a protein using a host cell as described in claim 1 of the same application. Although the specific method of making the host cell in claim 1 of the ‘855 application is not identical to the method of making the host cell as recited in claim 67 of the instant invention, the key element is the host cell that is used, and not the method of making the host cell. In both the ‘855 application and in the instant case, the host cell is made by complementation of a conditionally essential non-functional gene, whereby the host cell generated comprises at least two copies of a gene of interest in a chromosome (Note: in the ‘855 application, the gene of interest is contained in the amplification unit).

The methods of using the host cell to make a protein as indicated in claim 67 of the instant application are obvious in view of claim 59 of the ‘855 application, because the same

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type of host cell (although made by a slightly different method) can be used to make a protein in the claims of the ‘855 application. Furthermore, it would have been obvious to combine the limitations of claims 4, 16, 17 and 19 with claim 59 of the ‘855 application to arrive at claims 68 and 71-76 of the instant application because the limitations of those claims are applicable to the host cells used in the method of making a protein in the same manner as they are in the ‘855 application. One would have been motivated to make a protein by the method of claim 67 because a method of using the same types of cells is claimed by the method of claim 59 in the ‘855 application. Furthermore, one would have been motivated to combine the limitations of claim 59 with those of claims 4, 16, 17 and 19 to arrive at claims 68 and 71-76 in order to provide full patentable coverage of the types of cells that could be used to produce a protein of interest. Given the teachings of the copending application and the level of skill of the ordinary skilled artisan at the time of the applicants’ invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Also, if both patents are issued and the patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the patent issued from the co-pending ‘855 application, then two different assignees would hold a patent to the same claimed invention and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 77, 78 and 81-86 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 16, 17 and 19 of

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copending Application No. 09/869,855 (US 2003/0044940; Rasmussen, as above; henceforth the ‘855 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 77, 78 and 81-86 of the instant application describes a method making a particular host cell, while the combination of claim 17 in view of claims 1, 4, 16, 17 and 19 of the ‘855 application describe a similar invention.

Claim 77 of the instant invention claims a method of making a bacterial host cell comprising at least two copies of a gene of interest stably integrated into the chromosome of a host cell by introducing the gene of interest in the chromosome by complementing a non-functional conditionally essential gene with a corresponding conditionally essential non-functional gene through a recombination event which not only repairs the non-functional gene so that it is functional, but also integrates the gene of interest into the host chromosome. Claim 1 of the ‘855 application describes a similar process, except that a) the non-functional conditionally essential gene that is located in the host chromosome is repaired by recombination with a fully functional copy of that gene as represented on the integrating nucleic acid and b) the host cell is explicitly made susceptible to an inhibitory compound by the non-functional mutation. However, claim 17, which is dependent on claim 1, indicates that the integrating copy of the conditionally essential gene can also be a non-functional copy, therefore the only limitation that is not explicitly met is the susceptibility of the host cell to an inhibitory compound. Significantly, the ‘855 application indicates that the most preferred embodiment of a host cell having a non-functional mutation that renders a cell susceptible to an inhibitory compound has a mutation in the *galE* gene (see for example page 20, lines 10-11), which is also a most preferred embodiment of the instant invention (see for example page 5, line 24 and page 18, lines 23-24).

Therefore, the inventions are obvious in view of their preferred embodiments and in view of the combination of depending claims.

The limitations of claims 1 and 17 of the '855 application can reasonably and obviously be combined because claim 17 depends from claim 1. Furthermore, the most preferred embodiment of the invention claimed in the '855 application cites using the galE gene, which is also a most preferred embodiment of the instant invention of claims 77, 78 and 81-86, thus the claims are obvious in view of the most preferred embodiments of the claimed inventions.

Similarly, it would be obvious to combine the limitations of claim 17 with those in claims 4, 16, 17 and 19 because those claims are also dependent on claim 1, thus their limitations would obviously regard claim 17 by association. Since the combination of the limitations of claims 1, 4, 16, 17 and 19 of the '855 invention result in the invention of claims 77, 78, and 81-87 of the instant invention in view of the most preferred embodiments of the inventions, the invention of claims 77, 78, and 81-87 of the instant application are obvious in view of claims 1, 4, 16, 17 and 19 of the '855 patent. One would have been motivated to combine these teachings because one would certainly want to use the most preferred embodiments of the claimed inventions.

Furthermore, one would be motivated to combine the limitations of the dependent claims in order to ensure full protection of the disclosed invention of cells that could be generated by the described method. Given the teachings of the copending application and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Also, if both patents are issued and the patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the patent issued from

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the co-pending '855 application, then two different assignees would hold a patent to the same claimed invention and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson

July 28, 2003

David A. Lambertson
PATENT EXAMINER
A.Y.1636